# Clinical features of large cell neuroendocrine carcinoma: a population-based overview

# Clinical features of large cell neuroendocrine carcinoma: a population-based overview

Jules L. Derks[1], Lizza E. Hendriks[1], Wieneke A. Buikhuisen[2], Harry J.M. Groen[3], Erik Thunnissen[4], Robert-Jan van Suylen[5], Ruud Houben[6], Ronald A. Damhuis[7], Ernst J.M. Speel[8] and Anne-Marie C. Dingemans[1]

**Affiliations**: [1]Dept of Pulmonary Diseases, GROW School for Oncology and Developmental Biology, Maastricht University Medical Centre, Maastricht, The Netherlands. [2]Dept of Thorax Oncology, Netherlands Cancer Institute, Amsterdam, The Netherlands. [3]Dept of Pulmonary Diseases, University of Groningen and University Medical Centre, Groningen, The Netherlands. [4]Dept of Pathology, VU University Medical Centre, Amsterdam, The Netherlands. [5]Dept of Pathology, Jeroen Bosch Hospital, s' Hertogenbosch, The Netherlands. [6]Dept of Radiation Oncology, MAASTRO Clinic, Maastricht, The Netherlands. [7]Dept of Registry and Research, Comprehensive Cancer Centre, Rotterdam, The Netherlands. [8]Dept of Pathology, GROW School for Oncology and Developmental Biology, Maastricht University Medical Centre, Maastricht, The Netherlands.

**Correspondence**: Anne-Marie C. Dingemans, Dept of Pulmonology, P. Debyelaan 25, Postbox 5800, 6202 AZ, Maastricht, The Netherlands. E-mail: a.dingemans@mumc.nl

ABSTRACT Pulmonary large cell neuroendocrine carcinoma (LCNEC) is an orphan disease and few data are available on its clinical characteristics. Therefore, we analysed LCNEC registered in the Netherlands Cancer Registry, and compared data with small cell lung carcinoma (SCLC), squamous cell carcinoma (SqCC) and adenocarcinoma (AdC).

Histologically confirmed LCNEC (n=952), SCLC (n=11 844), SqCC (n=19 633) and AdC (n=24 253) cases were selected from the Netherlands Cancer Registry (2003–2012). Patient characteristics, metastasis at diagnosis (2006 or later), overall survival (OS) including multivariate Cox models and first-line treatment were compared for stage I–II, III and IV disease.

The number of LCNEC cases increased from 56 patients in 2003 to 143 in 2012, accounting for 0.9% of all lung cancers. Stage IV LCNEC patients (n=383) commonly had metastasis in the liver (47%), bone (32%) and brain (23%), resembling SCLC. Median OS (95% CI) of stage I–II, III and IV LCNEC patients was 32.4 (22.0–42.9), 12.6 (10.3–15.0) and 4.0 (3.5–4.6) months, respectively. Multivariate-adjusted OS of LCNEC patients resembled that of SCLC patients, and was poorer than those of SqCC and AdC patients. However, frequency of surgical resection and adjuvant chemotherapy resembled SqCC and AdC more than SCLC.

Diagnosis of LCNEC has increased in recent years. The metastatic pattern of LCNEC resembles SCLC as does the OS. However, early-stage treatment strategies seem more comparable to those of SqCC and AdC.

@ERSpublications
**Outcome of LCNEC is poor and metastatic pattern resembles SCLC, yet stage I–II treatment corresponds more with NSCLC** http://ow.ly/S37N9

Received: April 20 2015 | Accepted after revision: July 27 2015 | First published online: Nov 05 2015

Conflict of interest: None declared.

## Introduction

Large cell neuroendocrine carcinoma (LCNEC) is a high-grade carcinoma that expresses a neuroendocrine growth pattern (i.e. organoid, nesting, trabeculae, palisading cells or rosettes) and immunohistochemical neuroendocrine differentiation. In the third World Health Organization classification (2004), LCNEC was a subcluster of large cell carcinoma (LCC) and considered as part of the pulmonary neuroendocrine tumor (NET) spectrum. In the fourth WHO classification (2015), the diagnostic criteria for LCNEC were reproduced from those proposed in 1999 and LCNEC was moved from the LCC chapter to the NET chapter [1, 2]. Previous studies have shown that incidence of LCNEC is low, with a reported rate of 3% in surgically resected case series [3]. Nevertheless, according to the United States Cancer Registry (SEER) (2003–2007) and the Netherlands Cancer Registry (NCR) (1990–2010), pulmonary LCNEC incidence is rising [4, 5].

Because LCNEC expresses neuroendocrine features, it is suggested to treat LCNEC as small cell lung cancer (SCLC) [6, 7]. However, to date, no randomised trials investigating optimal treatment of LCNEC have been performed. Furthermore, it is unclear whether the LCNEC clinical presentation resembles non-small cell lung cancer (NSCLC) or SCLC. Recently, in the SEER registry, clinical characteristics of LCNEC (n=1211), SCLC (n=33 304) and LCC (n=8295) were compared. It was shown that compared to SCLC, LCNEC was more often diagnosed in an early stage and subsequently surgically treated, although data regarding adjuvant chemotherapy or specific stage III–IV disease treatment were not reported, as chemotherapy was not registered by SEER.

Series of surgically resected stage I–III lung cancer have shown that LCNEC and SCLC prognosis are similar [8, 9]. However, the SEER registry concluded that the prognosis of resected early-stage LCNEC resembled that of LCC and was superior to SCLC [4]. Two small studies in advanced LCNEC (n=25 and n=14) reported that overall survival (OS) of LCNEC was similar to that of SCLC [10, 11]. In one European phase II trial, OS of advanced LCNEC patients (n=29) was similar to results found in trials of advanced SCLC, while the response to chemotherapy was inferior for LCNEC compared to SCLC in a Japanese phase II trial (n=30) [12, 13].

Thus, from currently available data, it is not clear whether the LCNEC clinical presentation resembles SCLC or NSCLC. In addition, optimal treatment of LCNEC is not defined by current guidelines. The aim of this study was to evaluate the clinical presentation, prognosis and currently applied treatment of LCNEC in comparison to other lung cancer subtypes. Therefore, we analysed data from all histologically diagnosed LCNEC patients entered in the NCR, and compared those with both SCLC and NSCLC.

## Patients and methods

### *Data sources*

For this retrospective population-based study, data for patients diagnosed between 2003 and 2012 were obtained from the NCR. The registry has a nationwide coverage with >95% completeness of case ascertainment and patient data are collected in a standardised manner [14]. Furthermore, patients' records are linked to the Netherlands Pathology Registry and Centralized Civil Registry for pathology confirmation and annual vital status update.

Available data were year of diagnosis, histology (based on the International Classifications of Disease–Oncology (ICD-O), Third Edition), tumour grade, tumour–node–metastasis (TNM) classification (2010 or later: according to the TNM-7; 2009 or earlier: according to the TNM-6 classification) (generally, as clinical (c)TNM was overruled by pathological (p)TNM; in cases with neoadjuvant chemotherapy, cTNM overruled pTNM), first-line treatment modality and time from diagnosis till death or last follow-up. Metastatic sites at diagnosis (*i.e.*before treatment) were collected from documented clinical data (cTNM and/or pTNM) with a maximum of three separate locations. Subsequently, sites of metastases were combined into organ-specific subcodes (*e.g.* femur and rib into "bone").

### *Study population*

NCR data were retrieved on March 21, 2014, and included all patients with a histologically confirmed diagnosis of LCNEC (ICD-O code 8013), SCLC (8041–8043), SqCC (8050–8084) or AdC (8140–8230, 8250–8550 or 8570–8574), diagnosed between January 1, 2003, and December 31, 2012. AdC cases with neuroendocrine differentiation (ICD-O-3 code 8574) were clustered into AdC to prevent inclusion of tumours with neuroendocrine differentiation but without neuroendocrine morphology into the LCNEC cohort. LCNEC cases classified as grade I–II tumours were not included to avoid possible contamination with carcinoid tumours. In addition, LCC (not otherwise specified) was omitted as recent evidence suggests that up to 80% can be classified as SqCC or AdC upon revision in conjunction with immunohistochemical and molecular profiling [15, 16]. Other exclusion criteria were no recorded TNM classification, metachronous lung cancer or incomplete survival data.


DOI: 10.1183/13993003.00618-2015

To evaluate the clinical characteristics, metastatic pattern, first-line treatment and OS, several subcohorts were composed: all stages, stage I–II, stage III and stage IV disease. Additionally, first line treatment was compared separately for patients entered from 2010 to 2012 in order to observe possible temporal and TNM-6 to TNM-7 transition effects. For metastatic pattern analysis, additional exclusion criteria were applied: diagnosis before 2006 (since 2006, the metastasis locations were recorded systematically (⩾97%)), no documentation of metastatic sites, previous malignancy diagnosed within 5 years of lung cancer diagnoses and patients with stage IV disease classified according to TNM-6 solely based on pulmonary metastases (possibly T4 in TNM-7, *i.e.* no stage IV disease). Finally, prevalence of pleural metastasis was only analysed in patients classified according to TNM-7 to prevent underrating, as TNM-6 recorded pleural metastasis as IIIB disease and it was not feasible to reclassify this patient group.

This study was approved by the data monitoring committee and the medical ethical board of Maastricht University Medical Center (Maastricht, The Netherlands). Analyses were performed according to NCR guidelines and national privacy regulations.

### *Statistical analysis*

Incidence of LCNEC was calculated as fraction of the reported lung cancer incidence [17]. The Chi-squared and Fisher's exact test were used to compare categorical data and confidence intervals of proportions were calculated with the Wald (asymptotic) method. Medians of continuous variables were compared with a Mann–Whitney U-test. Censoring took place at the closing date (December 31, 2012) or at the last date of follow-up if patients emigrated. OS was calculated according to the Kaplan–Meier method and tested with the log-rank test. To examine effects of histology on survival, several stratified multivariate Cox regression analysis models were constructed including the covariates age, sex, histology, TNM (7 *versus* 6), N stage and T stage, and depending on the stage, treatment was included. Assumptions of proportional hazards were investigated by visual inspection of the complementary log–log plots. In cases where a hazard ratio (HR) was nonproportional, time-dependent HRs were reported at the cut-off point where nonproportionality started to influence the results. Two sided p-values <0.05 were considered significant. Analyses were performed using SPSS (version 22; IBM, Armonk, NY, USA).

TABLE 1 Baseline characteristics according to morphological subtype

| Variable | Histology | | | | p-value *versus* LCNEC | | |
|---|---|---|---|---|---|---|---|
| | LCNEC | SCLC | SqCC | AdC | SCLC | SqCC | AdC |
| **Patients n** | 952 | 11 844 | 19 633 | 24 253 | | | |
| **Age years** | | | | | | | |
| Mean±SD | 65.5±10.5 | 66.7±9.7 | 68.8±9.4 | 64.6±10.7 | | | |
| Median (IQR) | 66 (52–80) | 67 (53–81) | 70 (57–83) | 65 (49–81) | 0.14# | <0.001# | <0.001# |
| **Sex** | | | | | 0.01 | <0.001 | <0.001 |
| Male | 595 (62.5) | 6903 (58.3) | 15 055 (76.7) | 13 404 (55.3) | | | |
| Female | 357 (37.5) | 4941 (41.7) | 4578 (23.3) | 10 849 (44.7) | | | |
| **TNM stage** | | | | | <0.001 | <0.001 | <0.001 |
| I | 162 (17.0) | 370 (3.1) | 4745 (24.2) | 5318 (21.9) | | | |
| II | 90 (9.5) | 223 (1.9) | 2497 (12.7) | 1705 (7.0) | | | |
| III | 186 (19.5) | 3389 (28.6) | 7009 (35.7) | 5134 (21.2) | | | |
| IV | 514 (54.0) | 7862 (66.4) | 5382 (27.4) | 12 096 (49.9) | | | |
| Tumour stage | | | | | <0.001 | <0.001 | 0.002 |
| T1 | 183 (19.2) | 879 (7.4) | 2665 (13.6) | 5394 (22.2) | | | |
| T2 | 297 (31.2) | 3234 (27.3) | 7886 (40.2) | 7903 (32.6) | | | |
| T3 | 118 (12.4) | 1077 (9.1) | 2890 (14.7) | 2570 (10.6) | | | |
| T4 | 266 (27.9) | 4933 (41.6) | 5607 (28.6) | 6650 (27.4) | | | |
| Tx | 88 (9.2) | 1721 (14.6) | 585 (2.9) | 1736 (7.2) | | | |
| Nodal stage | | | | | <0.001 | <0.001 | 0.03 |
| N0 | 359 (37.7) | 2042 (17.2) | 8616 (43.9) | 10 227 (42.2) | | | |
| N1 | 96 (10.1) | 509 (4.3) | 2289 (11.7) | 2033 (8.4) | | | |
| N2 | 314 (33.0) | 6023 (50.9) | 6478 (33.0) | 7645 (31.5) | | | |
| N3 | 183 (19.2) | 3270 (27.6) | 2250 (11.5) | 4348 (17.9) | | | |

Data are presented as n (%) unless otherwise stated. LCNEC: large cell neuroendocrine carcinoma; SCLC: small cell lung carcinoma; SqCC: squamous cell carcinoma; AdC: adenocarcinoma; IQR: interquartile range; T: tumour; N: node; M: metastasis. #: Mann–Whitney U-test.

## Results

Between 2003 and 2012, 59 283 patients with LCNEC, SCLC, SqCC or AdC were entered in the NCR, of whom 56 682 patients were eligible for all-stage analysis (table 1) and 16 537 patients for metastatic site analysis (CONSORT flow diagram in figure 1). 999 (1.7%) out of 59 283 histologically selected patients were diagnosed with LCNEC, of whom 952 were eligible for the study. The total incidence of LCNEC as proportion of all lung cancers was 0.9%. Annual occurrence of LCNEC increased by 255% from 56 cases in 2003 to 143 in 2012 (figure 2a and b) with the sharpest increase in 2008. The percentage of LCNEC diagnosed in stage IV disease increased significantly over time: from 45.0% (n=144) in 2003–2007 to 58.5% (n=370) from 2008 onwards ($p<0.001$) (figure 2c).

### *Differences in baseline clinical characteristics*

Baseline clinical characteristics are presented in table 1. In LCNEC, 63% were male and the mean±SD age was 65.5±10.5 years. Compared to LCNEC, the stage distribution of SCLC was more advanced and SqCC was more frequent diagnosed as early disease. With the exception of a lower percentage of stage I disease, LCNEC stage distribution was comparable to AdC. Nodal stage (N)2–N3 disease was present in 52% of

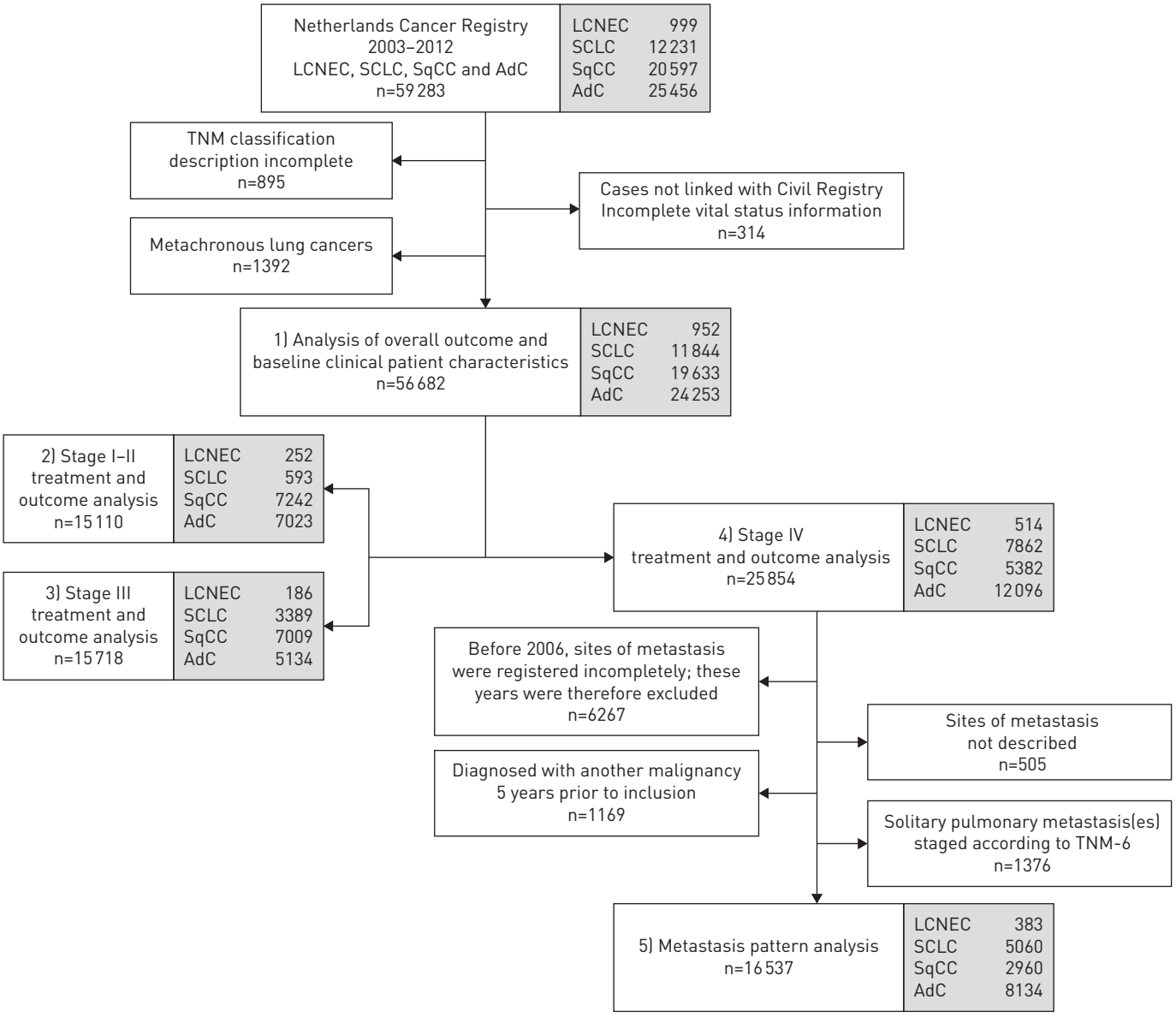


FIGURE 1 A CONSORT diagram is presented that describes the selection of cases from the Netherlands Cancer Registry. Patients with histopathologically diagnosed lung cancer during 2003–2012 were included if diagnosis was according to one of the following morphology codes: large cell neuroendocrine carcinoma (LCNEC) (8013), small cell lung carcinoma (SCLC) (8041–8043), squamous cell carcinoma (SqCC) (8050–8084) and adenocarcinoma (AdC) (8140–8230, 8250–8550 or 8570–8574). TNM: tumour–node–metastasis.


DOI: 10.1183/13993003.00618-2015

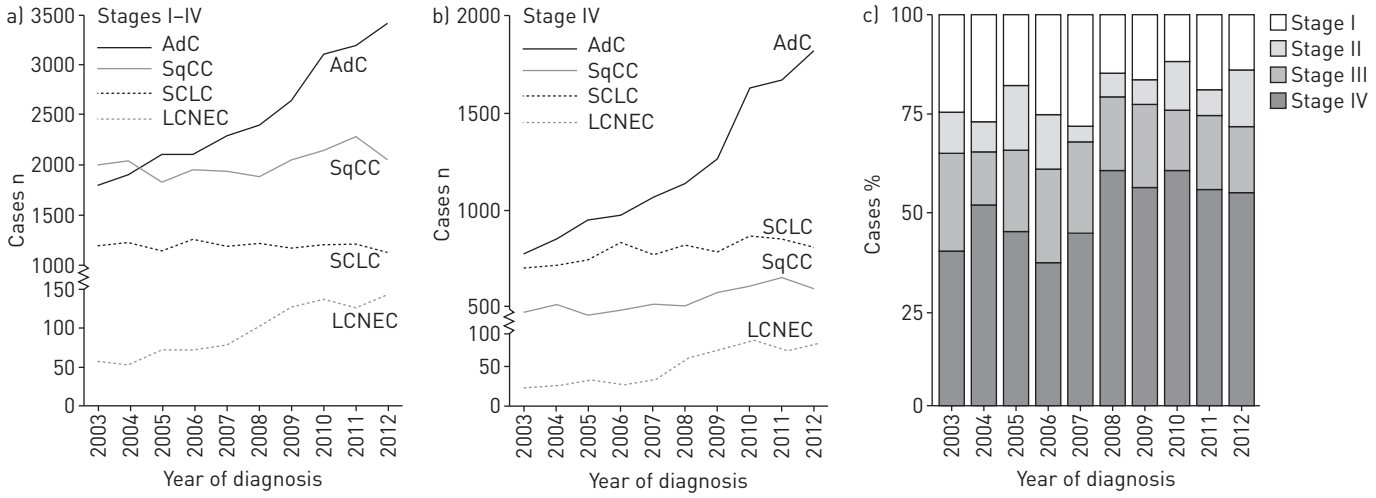


FIGURE 2 Incidence of histopathologically diagnosed cases of lung cancer registered in the Netherlands Cancer Registry during 2003–2012. a) Trend in frequency of individual morphological subtypes. b) Trend in frequency of individual morphological subtypes with stage IV. c) Trend in stage distribution of large cell neuroendocrine carcinoma (LCNEC) between 2003 and 2012. AdC: adenocarcinoma; SqCC: squamous cell carcinoma; SCLC: small cell lung carcinoma.

LCNEC, 79% of SCLC (p<0.001), 45% of SqCC (p<0.001) and 49% of AdC (p=0.10). In stage IV patients, the incidence of N2–N3 disease was significantly lower in LCNEC (69%) than in SCLC (80%) (p<0.001) and was comparable to SqCC (66%, p=0.30) and AdC (66%, p=0.34).

### *Prevalence of organ-specific metastasis at diagnosis*

LCNEC metastasis occurred in liver (47%), bone (32%), brain (23%), adrenal gland (19%), lung (14%), pleura (7%) and extrathoracic lymph nodes (16%) (figure 3). LCNEC had significantly fewer liver and more brain metastasis than SCLC. The prevalence of metastasis was not statistically different in the other organs. Patients with LCNEC had significantly fewer pleural and lung metastasis but more frequent liver and extrathoracic lymph node metastasis than patients with SqCC and AdC. Patients with LCNEC had more brain metastasis than those with SqCC, which was similar in AdC, whereas bone metastasis in LCNEC occurred less commonly than in patients with AdC.

### *Comparison of outcome*

The median (range) follow-up of the whole cohort was 52 (0–120) months. Median OS (95% CI) of LCNEC was 8.7 (7.9–9.6), SCLC 7.1 (6.9–7.3), SqCC 13.1 (12.7–13.4) and AdC 11.8 (11.5–12.2) months, respectively (figure 4). Median OS of stage I–II, III and IV LCNEC was 32.4 (22.0–42.9), 12.6 (10.3–15.0) and 4.0 (3.5–4.6) months, respectively, and that of stage IV chemotherapy-treated LCNEC was 7.7 (6.8–8.6) months. Table 2 depicts the models used for multivariate analysis of OS. Nonproportionality was observed for the covariate histology in stage I–II (figure 4b) and, therefore, HRs were calculated separately (*i.e.* HR for LCNEC differed between time period of ⩽10 months and >10 months). Patient variable adjusted OS of stage I–II LCNEC was superior to that of SCLC (⩽10 months and >10 months: HR (95% CI) 1.85 (1.27–2.69) and

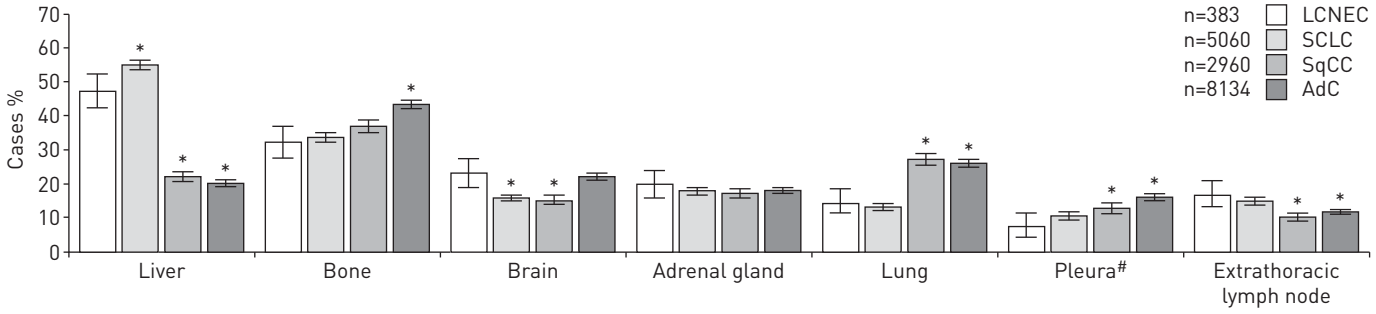


FIGURE 3 Prevalence of sites of metastases at primary diagnosis of lung cancer recorded between 2006 and 2012. Metastatic sites are clustered into organ-specific locations and analysed for each lung cancer subtype. All subtypes are compared with large cell neuroendocrine carcinoma (LCNEC). Error bars represent standard deviations. SCLC: small cell lung carcinoma; SqCC: squamous cell carcinoma; AdC: adenocarcinoma. #: analysed only in TNM-7. *: p<0.05 by Chi-squared test.

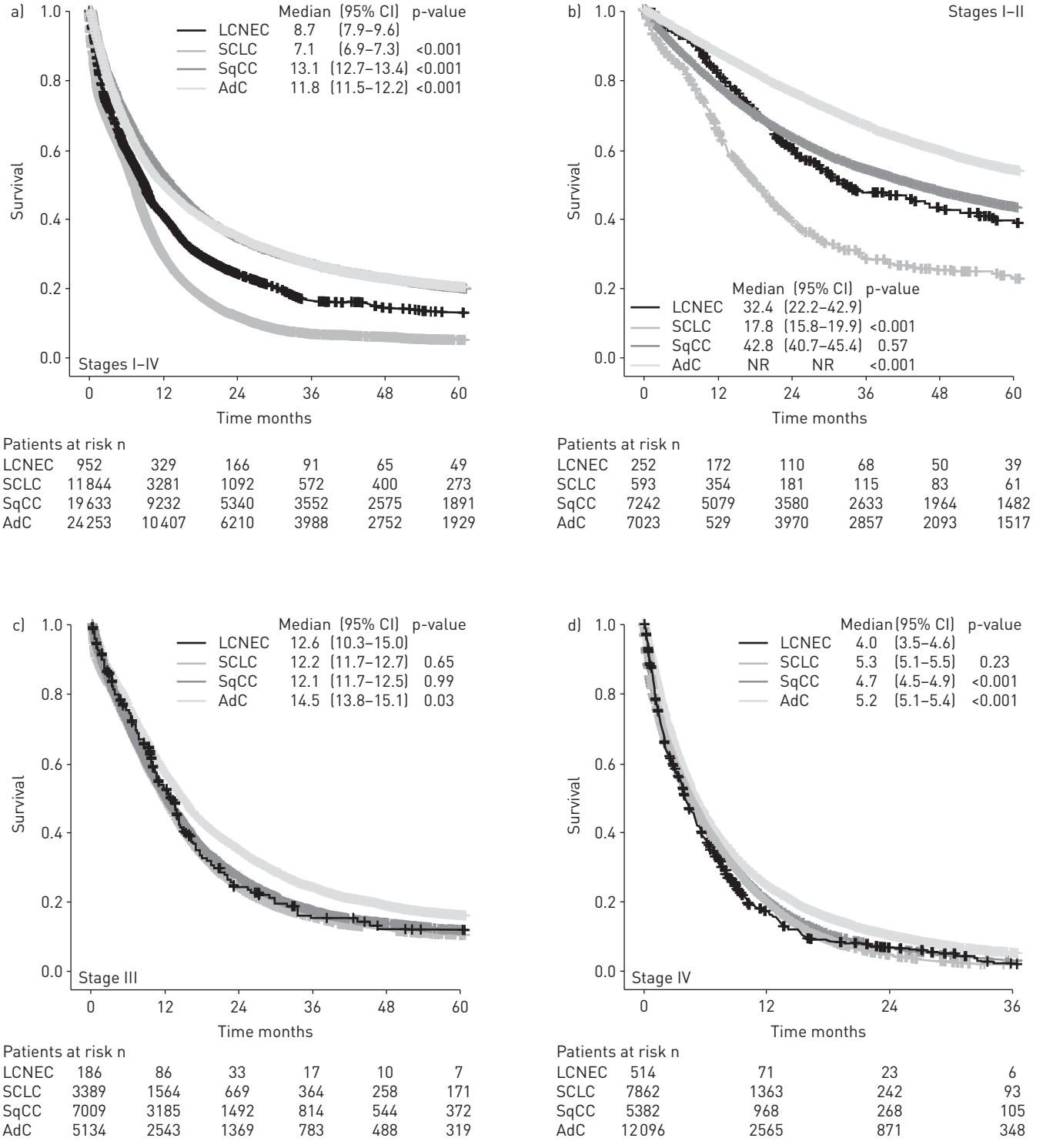


FIGURE 4 Survival curves for large cell neuroendocrine carcinoma (LCNEC) compared to small cell lung carcinoma (SCLC), squamous cell carcinoma (SqCC) and adenocarcinoma (AdC) in a) all stages (I–IV), and for stages b) I–II, c) III and d) IV separately. NR: not reached.

1.56 (1.21–2.00), respectively). Compared to LCNEC, OS of SqCC and AdC was only significantly better after 10 months (HR 0.65 (0.52–0.80) and 0.64 (0.52–0.80)). A separate model analysing patients treated with surgery showed no statistical difference between LCNEC and SCLC, yet the OS of SqCC and AdC showed similar results to the overall model. In stage III disease, the adjusted model showed no statistically significant difference between LCNEC and SCLC, SqCC or AdC. In stage IV, the adjusted model revealed that the OS of LCNEC was worse than that of SCLC (HR 0.87 (0.79–0.95)), SqCC (HR 0.79 (0.72–0.87)) and


DOI: 10.1183/13993003.00618-2015

TABLE 2 Univariate and multivariate analysis of overall survival for large cell neuroendocrine carcinoma (LCNEC) compared to small cell lung carcinoma (SCLC), squamous cell carcinoma (SqCC) and adenocarcinoma (AdC)

| Stage comparison | Variable | Histology | | | |
|---|---|---|---|---|---|
| | | LCNEC | SCLC | SqCC | AdC |
| **Stage I–II** | Unadjusted | | | | |
| | <10 months[¶] | 1 | 2.16 (1.49–3.15) | 1.43 (1.01–2.02) | 0.76 (0.54–1.08) |
| | ⩾10 months[¶] | 1 | 1.62 (1.27–2.08) | 0.75 (0.60–0.94) | 0.56 (0.45–0.70) |
| | Adjusted[+] | | | | |
| | <10 months[¶] | 1 | 1.85 (1.27–2.69) | 1.15 (0.82–1.63) | 0.84 (0.59–1.19) |
| | ⩾10 months[¶] | 1 | 1.56 (1.21–2.00) | 0.65 (0.52–0.80) | 0.64 (0.52–0.80) |
| Surgical cohort | Adjusted[§] | | | | |
| | <10 months[¶] | 1 | 0.71 (0.33–1.50) | 0.72 (0.49–1.05) | 0.56 (0.38–0.82) |
| | ⩾10 months[¶] | 1 | 1.14 (0.77–1.69) | 0.47 (0.37–0.60) | 0.52 (0.41–0.66) |
| **Stage III**[#] | Unadjusted | 1 | 1.04 (0.88–1.23) | 1.00 (0.84–1.18) | 0.83 (0.70–0.98) |
| | Adjusted[+] | 1 | 0.93 (0.78–1.10) | 0.88 (0.74–1.04) | 0.86 (0.73–1.02) |
| **Stage IV** | Unadjusted | 1 | 0.94 (0.86–1.04) | 0.88 (0.80–0.97) | 0.76 (0.70–0.84) |
| | Adjusted[+] | 1 | 0.87 (0.79–0.95) | 0.79 (0.72–0.87) | 0.79 (0.72–0.86) |
| Chemotherapy cohort | Adjusted[+] | 1 | 1.06 (0.91–1.23) | 0.85 (0.73–0.99) | 0.85 (0.73–0.99) |

Data are presented as hazard ratio (95% CI). [#]: insufficient patients with LCNEC therapeutically treated (*e.g.* with chemoradiotherapy or chemotherapy) to allow controlling for treatment; [¶]: time stratification used to counter nonproportionality (occurring for stage I–II); [+]: for age, sex, tumour–node–metastasis (TNM) edition, T stage and N stage; [§]: for age, sex, TNM edition, T stage, N stage and adjuvant chemotherapy.

AdC (HR 0.79 (0.72–0.86)). However, in patients treated with chemotherapy, the OS of LCNEC was similar to that of SCLC while the OS of SqCC and AdC remained significantly longer.

### *Comparison of first-line treatments*

Stage I–II LCNEC was generally treated with surgical resection (87.3%), as was AdC (p=0.09), but fewer resections were performed in SCLC (p<0.001) and SqCC (p<0.001) (table 3). Adjuvant chemotherapy was administered to 23.2% of LCNEC patients, which was less than in SCLC (p<0.001) but more frequent than in SqCC (p<0.001) and AdC (p<0.001). Patients with stage III LCNEC were treated with a combination of chemotherapy and radiotherapy (30.6%), surgical resection (21.0%), chemotherapy (14.5%) or received no treatment (19.4%). Treatment practice differed significantly from SCLC (p<0.001) but was comparable to SqCC (p=0.15) and AdC (p=0.10). In stage IV, 45.7% of LCNEC patients received no treatment, which was more frequent than in SCLC and AdC (p<0.001), and comparable to SqCC (p=0.76). Chemotherapy was administered in 38.1% of LCNEC patients. This was significantly less than in SCLC (p<0.001), more than in SqCC (p<0.001) and was equal to AdC (p=0.65). To explore whether the time period affected first-line treatment, the time period of 2010–2012 was analysed separately and compared to 2003–2009 but reported trends remained consistent (data not shown).

## Discussion

In this population-based study we confirmed that LCNEC is a rare disease with an average incidence of 0.9% of lung cancer over a 10-year period, while occurrence increased 2.5-fold. The presented results indicate that LCNEC is a highly aggressive form of lung cancer like SCLC, with a poor prognosis in all stages of disease. Nevertheless, there were important differences from SCLC: in stage IV, the prognosis of LCNEC was lower than SCLC, yet similar in selected cases treated with chemotherapy, as well as the clinical presentation, such as the lower proportion of patients with mediastinal lymph node involvement and the currently applied treatment in early disease differed from SCLC.

The total incidence of LCNEC (0.9%) as fraction of all diagnosed lung cancer was lower than that reported by institutional surgical series (1.7–3.0%) [3, 7] but higher than that reported by the population based SEER registry (0.6%). Probably this is caused by differences in analysed time period (*i.e.* 2003–2007). Overall, lung cancer occurrence increased with 24% in the Netherlands (2003–2012), mainly attributed to the increase in AdC [17]. The increase observed in LCNEC, particularly occurring after 2008, might be explained by growing awareness among pathologists of this relatively new entity, although at that time, no new pathology guideline was published. Additionally, an increased use of immunohistochemical neuroendocrine markers (CD56, synaptophysin and chromogranin-A) in routine diagnostics and an

TABLE 3 First-line treatment according to morphological subtype

| Variable | Histology | | | | p-value *versus* LCNEC | | |
|---|---|---|---|---|---|---|---|
| | LCNEC | SCLC | SqCC | AdC | SCLC | SqCC | AdC |
| **Patients n** | 952 | 11 844 | 19 633 | 24 253 | | | |
| **Treatment in stage I–II** | | | | | <0.01 | <0.01 | 0.441 |
| No treatment | 4 (1.6) | 68 (11.5) | 564 (7.8) | 254 (3.6) | | | |
| Resection | 220 (87.3) | 114 (19.2) | 5039 (69.9) | 5816 (82.8) | | | |
| RT | 17 (6.7) | 26 (4.4) | 1008 (13.9) | 601 (8.6) | | | |
| CT and RT | 4 (1.6) | 270 (45.5) | 288 (4.0) | 109 (1.6) | | | |
| CT | 2 (0.8) | 94 (15.9) | 111 (1.5) | 55 (0.8) | | | |
| Other | 5 (2.0) | 21 (3.5) | 232 (3.2) | 188 (2.7) | | | |
| **Stage I–II resections** | | | | | <0.01 | <0.01 | <0.01 |
| Adjuvant CT | 51 (23.2) | 91 (75.4) | 769 (15.3) | 786 (13.5) | | | |
| **Treatment in stage III** | | | | | <0.01 | 0.15 | 0.10 |
| No treatment | 36 (19.4) | 473 (14.0) | 1346 (19.2) | 801 (15.6) | | | |
| Resection | 39 (21.0) | 32 (0.9) | 1066 (15.2) | 1254 (24.4) | | | |
| RT | 20 (10.8) | 55 (1.6) | 1120 (16.0) | 362 (7.1) | | | |
| CT and RT | 57 (30.6) | 1794 (52.9) | 2252 (32.1) | 1492 (29.1) | | | |
| CT | 27 (14.5) | 912 (26.9) | 888 (12.7) | 879 (17.1) | | | |
| Other | 7 (3.8) | 123 (3.6) | 337 (4.8) | 346 (6.7) | | | |
| **Stage III resections** | | | | | 0.02 | 0.43 | 0.75 |
| (Neo)adjuvant CT | 21 (53.8) | 26 (81.3) | 508 (47.7) | 707 (56.4) | | | |
| **Treatment in stage IV** | | | | | <0.01 | <0.01 | <0.01 |
| No treatment | 235 (45.7) | 2147 (27.3) | 2422 (45.0) | 4823 (39.9) | | | |
| Resection | 17 (3.3) | 7 (0.1) | 131 (2.4) | 363 (3.0) | | | |
| RT | 30 (5.8) | 49 (0.6) | 523 (9.7) | 435 (3.6) | | | |
| CT and RT | 22 (4.3) | 447 (5.7) | 325 (6.0) | 436 (3.6) | | | |
| CT | 196 (38.1) | 4941 (62.8) | 1744 (32.4) | 4735 (39.1) | <0.01 | <0.01 | 0.65 |
| Other[#] | 14 (2.7) | 271 (3.4) | 237 (4.4) | 1304 (10.8) | | | |

Data are presented as n (%) unless otherwise stated. LCNEC: large cell neuroendocrine carcinoma; SCLC: small cell lung carcinoma; SqCC: squamous cell carcinoma; AdC: adenocarcinoma; RT: radiotherapy; CT: chemotherapy. [#]: including targeted treatment (*e.g.* tyrosine kinase inhibitor).

increase in core/needle-biopsy sampling in order to obtain sufficient material for molecular testing (*i.e.* more tissue) have improved LCNEC diagnosis. In addition, indiscriminate use of markers with low specificity for neuroendocrine differentiation (*i.e.* CD56 or NSE) could have increased the diagnostic frequency on biopsy tissue specimens. Finally, introduction of the IASLC guideline for diagnosis of lung cancer on biopsies (2011) may have increased awareness of LCNEC diagnosis on biopsies. Currently, LCNEC on small biopsies is referred to as NSCLC, possibly LCNEC when a neuroendocrine morphology and neuroendocrine immunohistochemical staining is confirmed in a biopsy specimen [2, 18].

The clinical characteristics of LCNEC corresponded to that of SqCC and AdC closely in the early stage, whereas LCNEC overlapped with SCLC in metastatic disease. Not only this study but also the SEER registry reported that the stage distribution of LCNEC resembled NSCLC [4]. A possible explanation is that advanced LCNEC was underrepresented (*e.g.* pathologists recognise LCNEC in surgically resected tissue more easily and may overlook LCNEC when assessing biopsies). However, we also found that LCNEC patients presented less often with stage N2–N3 compared to SCLC, and this matched SqCC and AdC, also in stage IV disease. Therefore, it might well be that early-onset LCNEC does not metastasise as rapidly as SCLC, increasing the chance of diagnosis at an earlier stage, an observation that was recently also seen in genetically engineered mouse models [18]. Nonetheless, whenever LCNEC has metastasised, the metastatic pattern resembles SCLC. Unfortunately, the metastatic pattern could not be confirmed in other studies as numbers of included patients (n=22–86) were too small [3, 7, 19, 20].

Conflicting data are available in the literature with regard to prognosis of LCNEC. The OS of LCNEC in surgical case series was similar to that of SCLC [8, 9, 21], while the SEER registry showed that OS in very early (T1N0M0) LCNEC was comparable to LCC and better than SCLC [4]. Resembling the SEER results, we observed a clear OS difference between LCNEC and SCLC in early-stage disease, but whenever SCLC was surgically treated, OS resembled LCNEC. The prognostic results in stage IV chemotherapy-treated patients were in line with two small cohorts that compared OS of LCNEC and SCLC [10, 11] and overall OS of chemotherapy-treated LCNEC resembled OS of the European phase II trial [12].


DOI: 10.1183/13993003.00618-2015

At present, there are no guidelines that aid physicians in treating LCNEC but we have shown that over recent years, treatment corresponded to SqCC and AdC more closely than to SCLC. The difference in (adjuvant) chemotherapy treatment between LCNEC and SCLC in stage I–II and IV was considerable. Indeed, if LCNEC is considered equally aggressive as SCLC, one would expect the ratio of chemotherapy-treated patients to be similar. Moreover, in the adjusted multivariate Cox regression analysis, the prognosis of LCNEC was poorer than that of SCLC. After selection of chemotherapy-treated patients, the adjusted multivariate Cox regression showed a nonsignificant difference. This increase in prognosis might be an important sign of possible undertreatment of patients with stage IV LCNEC disease in the overall population, but requires further investigation.

Because of the rarity of LCNEC, the majority of data comes from single-centre, retrospectively diagnosed LCNEC series. In this study, for the first time, we describe the clinical manifestation and treatment of both early- and advanced-disease LCNEC in a large, population-based, histologically diagnosed cohort. Moreover, we were able to comprehensively define the metastatic pattern of LCNEC at diagnosis and to compare this with SCLC, SqCC and AdC. By doing this, we excluded possible interference from treatment, and by excluding patients with previous malignancies, we minimised confounding from other cancers.

The current study has several limitations. Although only histology-selected cases were included, it remains possible that several tumours diagnosed as LCNEC in this registry were incorrectly classified. In clinical trials, up to 25–27% of LCNEC diagnosed on biopsies was reclassified into NSCLC or SCLC after central revision [12, 13]. Furthermore, interobserver studies show poor agreement, underscoring the difficulty in delineating LCNEC from SCLC and NSCLC [22]. However, this population-based study mirrors daily practice. A consequence of the histological selection criteria is the observed relatively high fraction of early-stage NSCLC. Another limitation might be related to the sensitivity of the metastatic pattern analysis as registration of used modalities for diagnostic imaging was not mandatory. Finally, we were not able to transcribe TNM-6 into TNM-7, had no data on smoking status, and were not able to adjust for possible prognostic confounders such as comorbidities, performance score and weight loss, as these variables were not or insufficiently registered in the NCR.

In summary, LCNEC is increasingly encountered, especially in stage IV disease. We have shown that LCNEC in clinical practice is a different entity, resembling SqCC and AdC in early-stage disease but with a comparably poor prognosis and metastatic pattern to SCLC. Nonetheless, possible biological important differences were present, as LCNEC showed less lymphatic N2–N3 pattern than SCLC. In the near future, it is expected that the visibility of LCNEC will increase even more for physicians due to the separate mention of LCNEC in the pulmonary NET chapter of the fourth WHO classification and the recent introduction of criteria for the diagnosis "NSCLC, possible LCNEC" on biopsy specimens [2, 18]. Therefore, collaboratively structured international phase III trials are needed to investigate the role of adjuvant chemotherapy in early-stage disease and optimal disease management of advanced-stage LCNEC. Eventually, this research can lead to establishment of broadly accepted guidelines for the treatment of LCNEC.

## Acknowledgements

The findings of this study were previously presented at the ENETS (European Neuroendocrine Tumor Society) conference, March 11–13, 2015; and at the young investigators meeting of the North American Neuroendocrine Tumor Society conference, October 15–17, 2015.

## References

1 Travis WD, Colby TV, Corrin B, *et al.* Histological Typing of Lung and Pleural Tumours. 3rd Edn. Heidelberg, Springer, 1999.
2 Travis WD, Brambilla E, Burke AP, *et al.* WHO Classification of Tumours of the Lung, Pleura, Thymus and Heart. 4th Edn. Geneva, WHO, 2015.
3 Takei H, Asamura H, Maeshima A, *et al.* Large cell neuroendocrine carcinoma of the lung: a clinicopathologic study of eighty-seven cases. *J Thorac Cardiovasc Surg* 2002; 124: 285–292.
4 Varlotto JM, Medford-Davis LN, Recht A, *et al.* Should large cell neuroendocrine lung carcinoma be classified and treated as a small cell lung cancer or with other large cell carcinomas? *J Thorac Oncol* 2011; 6: 1050–1058.
5 Korse CM, Taal BG, van Velthuysen ML, *et al.* Incidence and survival of neuroendocrine tumours in the Netherlands according to histological grade: experience of two decades of cancer registry. *Eur J Cancer* 2013; 49: 1975–1983.
6 Sun JM, Ahn MJ, Ahn JS, *et al.* Chemotherapy for pulmonary large cell neuroendocrine carcinoma: similar to that for small cell lung cancer or non-small cell lung cancer? *Lung Cancer* 2012; 77: 365–370.
7 Rossi G, Cavazza A, Marchioni A, *et al.* Role of chemotherapy and the receptor tyrosine kinases KIT, PDGFRα, PDGFRβ, and Met in large-cell neuroendocrine carcinoma of the lung. *J Clin Oncol* 2005; 23: 8774–8785.
8 Asamura H, Kameya T, Matsuno Y, *et al.* Neuroendocrine neoplasms of the lung: A prognostic spectrum. *J Clin Oncol* 2006; 24: 70–76.
9 Rindi G, Klersy C, Inzani F, *et al.* Grading the neuroendocrine tumors of the lung: an evidence-based proposal. *Endocr Relat Cancer* 2014; 21: 1–16.
10 Shimada Y, Niho S, Ishii G, *et al.* Clinical features of unresectable high-grade lung neuroendocrine carcinoma diagnosed using biopsy specimens. *Lung Cancer* 2012; 75: 368–373.

11 Igawa S, Watanabe R, Ito I, *et al.* Comparison of chemotherapy for unresectable pulmonary high-grade non-small cell neuroendocrine carcinoma and small-cell lung cancer. *Lung Cancer* 2010; 68: 438–445.
12 Le Treut J, Sault MC, Lena H, *et al.* Multicentre phase II study of cisplatin-etoposide chemotherapy for advanced large-cell neuroendocrine lung carcinoma: the GFPC 0302 study. *Ann Oncol* 2013; 24: 1548–1552.
13 Niho S, Kenmotsu H, Sekine I, *et al.* Combination chemotherapy with irinotecan and cisplatin for large-cell neuroendocrine carcinoma of the lung: a multicenter phase II study. *J Thorac Oncol* 2013; 8: 980–984.
14 Visser O, Siesling S, van DJ. Incidence of cancer in the Netherlands 1999/2000. Utrecht, Vereniging van Integrale Kankercentra, 2003.
15 The Clinical Lung Cancer Genome Project (CLCGP) and Network Genomic Medicine (NGM). A genomics-based classification of human lung tumors. *Sci Transl Med* 2013; 5: 209ra153.
16 Rekhtman N, Tafe LJ, Chaft JE, *et al.* Distinct profile of driver mutations and clinical features in immunomarker-defined subsets of pulmonary large-cell carcinoma. *Mod Pathol* 2013; 26: 511–522.
17 Integraal Kankercentrum Nederland. Figures from the Netherlands Cancer Registry 2003–2012. www.cijfersoverkanker.nl/selecties/dataset_1/img547717e2db7cf
18 Travis WD, Brambilla E, Noguchi M, *et al.* International Association for the Study of Lung Cancer/American Thoracic Society/European Respiratory Society international multidisciplinary classification of lung adenocarcinoma. *J Thorac Oncol* 2011; 6: 244–285.
19 Iyoda A, Hiroshima K, Moriya Y, *et al.* Postoperative recurrence and the role of adjuvant chemotherapy in patients with pulmonary large-cell neuroendocrine carcinoma. *J Thorac Cardiovasc Surg* 2009; 138: 446–453.
20 Iyoda A, Jiang SX, Travis WD, *et al.* Clinicopathological features and the impact of the new TNM classification of malignant tumors in patients with pulmonary large cell neuroendocrine carcinoma. *Mol Clin Oncol* 2013; 1: 437–443.
21 Kinoshita T, Yoshida J, Ishii G, *et al.* The differences of biological behavior based on the clinicopathological data between resectable large-cell neuroendocrine carcinoma and small-cell lung carcinoma. *Clin Lung Cancer* 2013; 14: 535–540.
22 den Bakker MA, Thunnissen FB. Neuroendocrine tumours-challenges in the diagnosis and classification of pulmonary neuroendocrine tumours. *J Clin Pathol* 2013; 66: 862–869.



DOI: 10.1183/13993003.00618-2015